Adam Mecca

Project Title: *Investigation of molecular changes in mGluR5 and SV2A to study synaptic alteration in Alzheimer's disease using PET*

Requested Amount: $69,000

Contents

Vote Tabulations

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Reviewer Comments:

- Although the number of participants is too low to draw any definitive conclusions, this would serve as pilot data for a larger application. It is unfortunate that Yale exacts such high costs for research PET imaging.

ABF Letter of Intent

Letter of Intent Form

Prefix

First Name

Adam

Last Name

Mecca

Suffix

Title

Institution

Yale Unversity

Office Address

One Church Street
8th Floor

City

New Haven

State

CT

Postal Code

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203.764.8111

Project Details

Project Title

Investigation of molecular changes in mGluR5 and SV2A to study synaptic alteration in Alzheimer's disease using PET

General focus

Alzheimer’s & Dementia

Specific Disease Focus

Alzheimer's Disease Neurobiology

Project Description

Alzheimer's disease (AD) is a common and progressive illness that leads to impaired memory and thinking, impaired ability to function independently, and profound societal costs. This proposal seeks to expand the understanding of AD pathophysiology with the ultimate goals of

enhancing care by ensuring timely/accurate diagnosis, as well as preventing and effectively treating this disease. AD afflicts over 5 million people in the US and no current therapy modifies its course. Positron Emission Tomography (PET) imaging has been successfully employed to investigate changes in living humans at the molecular level, aiding in the diagnosis and understanding of AD. Therefore, the neurobiology of AD can be studied in vivo with multi-tracer neuroimaging and neuropsychological characterization.
Molecular changes at the synaptic level have been shown to be associated with AD, but the majority of molecular and synaptic investigations are performed in humans after death or in animal models. Metabotropic glutamate receptor subtype 5 (mGluR5) is present at synapses throughout the cortex and is a mediator of amyloid beta induced AD pathology. Therefore, mGluR5 is a candidate biomarker for AD and a target for therapeutic intervention, making its detection an important goal. Furthermore, synaptic vesicle glycoprotein 2A (SV2A) is a pre-synaptic protein with potential as the first in vivo marker of synaptic density. Since synaptic loss is observed in the earliest stages of AD, SV2A binding stands to be a robust marker of disease progression.
The objective of this proposal is to apply PET methods to understand the neurobiological changes associated with AD using [18F]FPEB, a specific ligand for mGluR5, and [11C]UCB-J, a specific ligand for SV2A (synaptic density). This is likely to have a significant impact by (i) determining the changes in mGluR5 receptor availability that occur during AD, (ii) determining the changes in synaptic density that are detectible during AD, and (iii) understanding the relationship between changes in mGluR5 receptor availability and synaptic density. These investigations will provide valuable understanding of the AD disease process and lead to the development of both novel treatments and therapeutic biomarkers.

How will your project contribute to the treatment, prevention or cure of a neurological disease(s)?

In summary, both synaptic and receptor level changes that occur with AD may be valuable biomarkers used in clinical trials to track therapeutic response and disease progression. Therefore, understanding of the receptor and synaptic level changes that occur due to Alzheimer's disease (AD) will provide valuable insights into the disease process and lead to the development of novel treatments.

Project Budget

Total expense budget

An estimated total is acceptable.

$140,000

Value of existing funding or in-kind support

What portion of the above total expense has funding already received or promised?

$71,000

Portion to be raised through crowdfunding

How much are you seeking from the crowdfunding platform?

$69,000

Attachments and Verifications

Please download, fill out, and upload the Financial Disclosures & Conflict of Interest form.

Financial Disclosures & Conflicts of Interest Form

Mecca_AP_Financial-Disclosure-Conflict-of-Interest-Form.pdf

CV of Principal Investigator

Mecca_CV_full_14March2017.pdf

I understand that the American Brain Foundation will not post approved projects for crowdfunding until documentation of IRB approval or exemption is provided.

Yes

ABF Full Application

Applicant Information

Prefix

First Name

Adam

Last Name

Mecca

Suffix

Title

Geriatric Psychiatry Fellow, Assistant Professor of Psychiatry (July 1, 2017)

Institution Name

Yale Unversity

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Project Details

Project Title

Investigation of molecular changes in mGluR5 and SV2A to study synaptic alteration in Alzheimer's disease using PET

Project Start Date

July 01, 2017

Project End Date

July 01, 2019

Disease focus

Alzheimer’s & Dementia

Specific Disease Focus

Alzheimer's Disease Neurobiology

Project Summary/Abstract

This proposal seeks to expand the understanding of Alzheimer's disease (AD) pathophysiology with the ultimate goals of enhancing care by ensuring timely/accurate diagnosis, as well as preventing and effectively treating AD. AD afflicts over 5 million people in the US and no current therapy modifies its course. Using Positron Emission Tomography (PET), the neurobiology of AD can be studied in vivo with multi-tracer neuroimaging.

Molecular changes at the synaptic level are associated with AD. Metabotropic glutamate receptor subtype 5 (mGluR5) is present at synapses throughout the cortex and is a mediator of amyloid □ induced AD pathology. Therefore, mGluR5 is a candidate biomarker for AD and a target for therapeutic intervention. Furthermore, synaptic vesicle glycoprotein 2A (SV2A) is a pre-synaptic protein with potential as the first in vivo marker of synaptic density. Since synaptic loss is observed in the earliest stages of AD, SV2A binding stands to be a robust marker of disease progression.

This proposal will apply PET methods to understand the neurobiological changes of AD using [18F]FPEB, a ligand for mGluR5, and [11C]UCB-J, a ligand for SV2A. This is likely to have a significant impact by (i) determining the changes in mGluR5 availability in AD (Aim 1), (ii) determining the changes in synaptic density in AD (Aim 2), and (iii) understanding the relationship between changes in mGluR5 availability and synaptic density (Aim 3). These investigations will provide valuable understanding of the AD disease process and lead to the development of both novel treatments and therapeutic biomarkers.

Project Narrative

Alzheimer's disease is a common and progressive illness that leads to impaired memory and thinking, impaired ability to function independently, and profound societal costs (loss of productivity, utilization of health care services, and a significant need of support from caregivers). To expand the basic understanding of Alzheimer's disease pathophysiology, this proposal aims to utilize two novel radioligands and Positron Emission Tomography imaging to characterize synaptic and receptor level changes that occur in disease. A clearer understanding of synapse and receptor level changes will provide valuable insights into the Alzheimer's disease process that lead to the development of both novel treatments and therapeutic biomarkers.

Facilities and Equipment

The Yale Alzheimer's Disease Research Unit (ADRU) is an established clinical research unit that has specialized in cognitive disorders and aging research for the past 21 years (~60 multicenter clinical trials). The ADRU is staffed by a geriatric psychiatrist (van Dyck, Director), a behavioral neurologist (Dr. Salardini), a neuropsychologist, a clinical research fellow (Dr. Mecca), four geriatric psychiatry fellows, a research psychologist, a nurse practitioner, and nine research assistants. The ADRU is an ADCS member site and houses the clinical core of the Yale Alzheimer's Disease Research Center, both funded by the NIA. The ADRU is a robust infrastructure for subject recruitment, as well as expertise in clinical research methodology.

The Yale PET Center is a state-of-the-art 16,000 sq. ft. facility that opened in July 2005. The PET Center has a GE PETtrace cyclotron, with targetry for producing C-11, F-18, N-13 and O-15 radioisotopes. Chemistry modules are available for the production of radiotracers. The Center has 6 scanners including the Siemens High Resolution Research Tomography (HRRT) scanner that will be used in this study (world's

highest-resolution human PET imaging camera). Two laboratories for blood and metabolite analyses are available. The Center also has an image analysis laboratory. Over 8,000 administrations of PET radiopharmaceuticals as part of quantitative in vivo PET studies have been performed with over 100 radiopharmaceuticals.
The Yale Magnetic Resonance Research Center operates two identically equipped, research-dedicated 3.0T Siemens Trio TIM systems, one of which will be used to perform MRI for this study.

Specific Aims

To address the existing gaps in current knowledge of the pathophysiology of synaptic- and receptor-level changes in AD, the following aims are proposed:
AIM 1. Investigate mGluR5 binding as a biomarker of AD. Utilizing PET and the radiotracers [18F]FPEB for mGluR5 and [11C]PiB for amyloid, mGluR5 binding will be quantified in a group of amyloid-positive individuals with clinical AD (MCI or dementia) compared to a healthy control (HC) group of amyloid-negative individuals with normal cognition (n = 20 per group).
AIM 2. Investigate SV2A binding as a biomarker of synaptic density in AD. Utilizing PET and the radiotracers [11C]UCB-J and [11C]PiB, synaptic density will be quantified in a group of individuals with clinical AD (MCI or dementia) compared to a HC group of individuals with normal cognition (n = 20 per group).
AIM 3. Investigate group and individual differences in mGluR5 binding in relation to synaptic density. Utilizing the data from the above aims, mGluR5 binding and SV2A density will be quantified and compared in a group of AD (n =20) and HC (n = 20) participants.
The central hypothesis is that mGluR5 and SV2A density will be reduced in AD with differing deficits in regional distribution and density between markers. This study is innovative because it explores the neurochemistry of AD in vivo in humans using two novel PET radiotracers. These investigations will provide valuable information that will contribute to the understanding of an ongoing disease process and lead to the development of both novel treatments and therapeutic biomarkers.

Research Strategy

Significance, Innovation, Approach, Timeline

1. Significance

The progression of AD is increasingly understood to occur along a continuum from pre-clinical AD, to mild cognitive impairment (MCI), and finally AD dementia(1). At all stages, the progression is coupled to a distinct pathology, with plaques of Amyloid-β (Aβ), neurofibrillary tangles of hyperphosphorylated Tau protein, and synaptic loss(2). Positron emission tomography (PET) has aided in the diagnosis and understanding of AD, by revealing molecular-level metabolic changes and Aβ in humans(3). Therefore, the neurobiology of AD can be investigated in vivo with the advantages of multi-tracer neuroimaging and robust neuropsychological characterization.

Synaptic loss is linked with AD progression and provides a novel target for exploration with PET(4). Synaptic changes are important biological markers of disease and potential therapeutic targets. For example, metabotropic glutamate receptor subtype 5 (mGluR5) is present post-synaptically, is a modulator of synaptic transmission(5-7), and mediates the synaptotoxic action of Aβ(8). Therefore, mGluR5 is a candidate biomarker for AD and a therapeutic target. Additionally, synaptic vesicle glycoprotein 2A (SV2A) binding measured with [11C]UCB-J PET is the first in vivo marker of synaptic density(9). Since mGluR5 links Aβ toxicity to synaptic loss that is observed in the earliest stages of AD, SV2A binding stands to be a robust marker of disease(10).

2. Innovation

• First-in-human AD studies of mGluR5 and SV2A in vivo.

• Comparison of [18F]FPEB and [11C]UCB-J allows us to test whether the loss of mGluR5 at the post synaptic density differs from decline in synaptic density.

• High-resolution brain PET with state-of-the-art methodology.

3. Approach

Imaging mGluR5 with [18F]FPEB. Parametric images of [18F]FPEB VT are of an excellent quality suitable for regional and whole-brain analysis methods(7). Preliminary experiments support the hypotheses that mGluR5 density is lower in individuals with AD. Cortical regions commonly affected by AD pathology had decreased binding in the AD participants (n=6) compared to HC participants (n=7), with the largest difference in the hippocampus (p=0.04) and a slightly reduced effect after PVC (p=0.06).

SV2A human imaging with [11C]UCB-J. Initial test-retest studies with [11C]UCB-J showed fairly homogenous uptake across GM regions, much lower white matter uptake, tissue activity curves well described by the 1 tissue compartment model, and specific SV2A binding(9). We have scanned one amyloid negative, cognitively normal older adult, as well as two amyloid positive amnestic MCI participants and one amyloid positive AD-dementia participant with [11C]UCB-J. Binding of [11C]UCB-J in the older adults was most distinctly reduced in hippocampus (compared to young controls), with a VT reduction of 29% in the older control, and more robust reductions of 27% and 54% in the 2 MCI participants, and 57% in the AD-dementia participant. Cortical VT values were also reduced. These data suggest that hippocampal SV2A binding is dramatically altered by aging and the AD-spectrum.

Screening Evaluation. Participant (age 55-90) will have a screening visit including informed consent, the Mini-Mental State Examination, Logical Memory Test, Clinical Dementia Rating Scale, and the Geriatric Depression Scale. A physical examination and screening laboratory tests will be performed.

Neuropsychological Assessment. Participants will have a neuro¬psychological evaluation.

MRI Methods. MRI will be obtained using a 3T Trio (Siemens Medical Systems, Erlangen, Germany).

PET Scan Methods. PET scans will be performed on the HRRT, the highest resolution human PET scanner. The [18F]FPEB scan will be acquired using administration of up to 5 mCi of tracer using a bolus/ infusion method. The [11C]UCB J scan will be acquired following administration of up to 20 mCi using bolus/infusion delivery.
AIM 1. Investigate mGluR5 binding as a biomarker of AD. A total of 20 AD participants and 20 age- and sex-matched HC participants will be scanned with [18F]FPEB. Our primary hypothesis is that compared to HC, [18F]FPEB will reveal decreased mGluR5 binding (VT) in AD using a composite cortical region and hippocampus. For Aim 1 and Aim 2, analyses will be performed using linear mixed models with diagnostic group as the main explanatory factor, sex as a fixed factor, age as a covariate, and matching group as a random factor.
AIM 2. Investigate SV2A binding as a biomarker of synaptic density in AD. A total of 20 AD participants and matched HC participants will be scanned with [11C]UCB-J. Our primary hypothesis is that compared to HC, [11C]UCB-J will reveal decreased synaptic density in AD.
AIM 3. Investigate group and individual differences in mGluR5 binding in relation to synaptic density. mGluR5 binding and SV2A density will be quantified and compared in a group of AD and HC participants (20 per group). Our primary hypothesis is that compared to HC participants, AD participants will have greater reductions in mGluR5 binding than SV2A binding using regional analysis, reflecting that mGluR5 is a more direct marker of Aβ mediated toxicity.
4. Timeline.
10-12 participants will complete the research protocol per year. This is feasible based on recruitment rates of the Yale ADRU and PET Center.

List up to 5 milestones you will reach within the first 6 months of your study.

1. Enroll 10 participants (5 HC and 5 AD) and complete the screening visit.
2. Complete [11C]PiB scan for 6 participants (3 HC and 3 AD).
3. Complete [18F]FPEB scan for 6 participants (3 HC and 3 AD).
4. Complete [11C]UCB-J scan for 6 participants (3 HC and 3 AD).
5. Complete neuropsychiatric testing visit for 6 participants (3 HC and 3 AD).
6. Refine analysis stream for regional and voxel-based analyses.

Age of Population Group(s) that will potentially benefit from this research

(check boxes that apply)

Seniors (65+)

Scientific Literature References

Reference 1

Sperling RA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the NIA-AA workgroups on diagnostic

guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-92. PMC3220946.

Reference 2

Jack CR, Jr., et al. Introduction to the recommendations from the NIA-AA workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):257-62. PMC3096735.

Reference 3

Klunk WE, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Annals of neurology. 2004;55(3):306-19. PMID: 14991808.

Reference 4

Selkoe DJ. Alzheimer's disease is a synaptic failure. Science (New York, NY). 2002;298(5594):789-91. PMID: 12399581

Reference 5

Daggett LP, et al. Molecular and functional characterization of recombinant human metabotropic glutamate receptor subtype 5. Neuropharmacology. 1995;34(8):871-86. PMID: 8532169

Reference 6

Ohnuma T, et al. Expression of the human excitatory amino acid transporter 2 and mGluRs 3 and 5 in the prefrontal cortex from normal individuals and patients with schizophrenia. Brain Res Mol Brain Res. PMID: 9602129

Reference 7

Sullivan JM, et al. Kinetic analysis of the metabotropic glutamate subtype 5 tracer [(18)F]FPEB in bolus and bolus-plus-constant-infusion studies in humans. J Cereb Blood Flow Metab. 2013;33(4):532-41. PMC3618388

Reference 8

Kaufman AC, et al. Fyn inhibition rescues established memory and synapse loss in Alzheimer mice. Annals of neurology. 2015. PMID: 25707991

Reference 9

Finnema SJ, et al. Imaging synaptic density in the living human brain. Sci Transl Med. 2016;8(348):348ra96. PMID: 27440727

Reference 10

Pham E, et al. Progressive accumulation of amyloid-beta oligomers in AD and in amyloid precursor protein transgenic mice is accompanied by selective alterations in synaptic scaffold proteins. FEBS J. PMCID: 2933033

Budget, Attachments and Acknowledgements

Budget

We recognize that changes may have occurred since the time you submitted your Letter of Intent. Please share the most recent accurate numbers below:

Total Project Budget

$145,080

Total existing funding or in-kind support

$76,080

Amount to be raised through crowdfunding campaign

$69,000

Evidence of institutional support (letter)

Mecca Institution Letter.pdf

Full budget

budget.docx

Documentation of IRB/IUCAC approval or exemption, if applicable.

hic_approval.pdf

Completed conflict of interest & disclosure form

Mecca_AP_Financial-Disclosure-Conflict-of-Interest-Form.pdf

I understand that the ABF will not list approved projects for general public crowdfunding campaigns until documentation of IRB/IUCAC approval or exemption is provided.

Yes

I understand that approval of the project to be shared on the crowdfunding campaign site is dependent on providing and working with the ABF staff to create the requisite materials that present the project in an engaging, easy-to-understand website presentation. I am amenable to working with the ABF staff to create such materials.

Yes

I understand that approval once a project has been completed, I will be required to submit a summary of my findings to be posted online (one page), and will submit this in a reasonably timely fashion. I also agree to submit a financial report, and to co-sign a thank you letter with the ABF that will be sent to donors.

Yes

I understand and agree that the ABF may share the information that I provide (including but not limited to the project description and relevant biographical/background details) in conversations with other potential funders outside the website to bolster fundraising efforts.

Yes

American Brain Foundation Release Agreement

American Brain Foundation
Release Agreement – Research

1. **Grant**. For good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I grant to the American Brain Foundation ("ABF") and to the ABF's affiliates (including the American Academy of Neurology), and their respective contractors, agents, assigns, licensees, and successors (collectively, the "ABF Group"), a worldwide, royalty-free, perpetual, irrevocable right to take and use my image, likeness, voice, verbal statements, written testimonials and name and all images, videos, sound recordings, and written and verbal materials that I provide to the ABF (collectively, the "Materials "), in all forms

and media, including composite or modified representations, for the purpose of promoting and supporting the missions of the ABF. For the avoidance of doubt, the Materials include all research project proposal information, project reports and other research-related information submitted to the ABF. I understand and agree that the ABF may publish the Materials on any and all media, including printed matter, promotional materials, e-mail, websites and social media platforms.

2. **Acknowledgement of Use**. I understand that the ABF Group may use the Materials on any and all media, including printed matter, promotional materials, e-mail, websites and social media platforms. I understand that the ABF's use of the Materials may intentionally or unintentionally give rise to the impression that either I or a family member suffers from brain/neurologic disease, and I nevertheless consent to this use. The ABF is not obligated to utilize any of the rights granted in this agreement. I waive the right to inspect or approve any uses of the Materials in connection with this grant.
3. **Warranty**. I warrant that I have the full power to enter into this agreement and to grant the aforementioned rights.
4. **Release**. I release the ABF Group from all liability for any claims that may arise regarding the use of Materials, including any claims of defamation, invasion of privacy, or infringement of moral rights, rights of publicity, or copyright. The ABF is permitted, although not obligated, to include my name as a credit in connection with any use of the Materials.**I have read and understood this agreement, I understand that it contains a release of liability, and I am over the age of 18**. This agreement expresses the complete understanding of the parties and shall be binding on me and my heirs, legal representatives and assigns. I understand that I am entering into a legally binding agreement and that clicking "I Accept" below shall have the same legal effect as my signature on this Release Agreement.

I Accept

BUDGET

PET/MRI scanning costs. This protocol will utilize PET and MRI data from 40 individuals each for Aim 1 and Aim 2 that are being collected during ongoing projects. It is expected that at least 75% of participants will complete the PET scans for both aims. In order to complete Aim 3, it is expected that approximately 30 subjects will co-enroll in the protocols for Aim 1 and 2. Therefore, an additional 10 subjects will be recruited to complete Aim 3 and funding for their PET scans and MRIs are being requested.

Therefore, funds are requested for 10 individuals will co-enroll and complete a screening visit, MRI, [^{11}C]PiB PET scan, [^{18}F]FPEB PET scan, [^{11}C]UCB-J PET scan, and neuropsychological testing visit. The cost of scans is currently $525 for each MRI, $5078 for each [^{11}C]UCB-J batch production plus scan and metabolite measurement, $4244 for [^{11}C]PiB synthesis and scan, and $4661 for each [^{18}F]FPEB batch production plus scan and metabolite measurement.

Participant payments. Funds are requested to compensate subjects for time and participation. Payments are $50 for screening visit assessments, $250 for each PET scan (3 scans), $50 for MRI, and $50 for neuropsychological testing assessments visit.

Item	Cost per subject	Subjects	Total
[11C]UCB-J	$5078	10	$50,780
[11C]PiB	$4244	10	$42,440
[18F]FPEB	$4661	10	$46,610
MRI	$525	10	$5,250
Total			$145,080
Funds Requested			**$69,000**

YALE UNIVERSITY
SCHOOL OF MEDICINE
DEPARTMENT OF PSYCHIATRY

JOHN H. KRYSTAL, M.D.
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March 28, 2017

Re: Letter of Institutional Committee: Adam Mecca, M.D., Ph.D.

Dear Review Committee Members,

As Chair of the Yale Department of Psychiatry, I enthusiastically confirm the Institutional and Department commitment for Dr. Mecca's American Brain Foundation crowdfunding campaign application entitled, "Investigation of molecular changes in mGluR5 and SV2A to study synaptic alteration in Alzheimer's disease using PET."

Dr. Mecca is a Geriatric Psychiatry Fellow and Research Fellow at the Yale Alzheimer's Disease Research Unit (ADRU). He is an extremely talented psychiatrist and an invaluable member of the ADRU Team. Upon completion of his training in June 2017, he will begin a tenure-track Assistant Professor position that would include the studies outlined in this proposal.

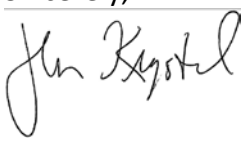
Prior to his fellowship, Dr. Mecca was a member of the Yale Psychiatry Residency Neuroscience Research Training Program (NRTP). This is a highly competitive program (1300 applicants for 16 positions) that we have developed to provide integrated clinical and research training during residency. I have personally followed Dr. Mecca's progress and invested in Dr. Mecca's career development through the NRTP. I will continue to do so as he moves to the next stage of his career.

Our Department is committed to Dr. Mecca's career. I will ensure that he has the necessary protected time, support, and assistance to complete the next critical phase of his career development development. We will provide the needed space, equipment, and other resources and facilities necessary to allow Dr. Mecca to complete this proposal. Dr. Mecca will devote ≥75% of his effort to the proposed research and career development activities. Our commitment to Dr. Mecca's career development is not contingent upon the receipt of a career development award.

Dr. Mecca is an integral part of our Department's research program, where he is mentored by Dr. Christopher van Dyck (Co-Director of our NIA ADRC and Director of the ADRU). Dr. Mecca's has two additional on-site mentors: Richard Carson, Ph.D. (PET), and Peter Van Ness, Ph.D. (biostatistics). Dr. Mecca will have extensive opportunities for formal and informal training in these areas through seminars, courses, and conferences. In addition, he will receive support and encouragement to seek additional funding opportunities, both extramural and intramural, which will promote collaborative work across departments and at other institutions.

We are extremely pleased that Dr. Mecca has chosen to begin his career at Yale. I believe that Dr. Mecca holds great promise of attaining an independent research career. We look forward to nurturing his growth and development.

Sincerely,



John H. Krystal, M.D.
Robert L. McNeil, Jr. Professor of Translational Research
Professor of Neuroscience

Yale University

Institutional Review Board
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New Haven CT, 06520-8327

Telephone: 203-785-4688
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To:	Christopher Van Dyck, M.D.
From:	**Yale University Institutional Review Board**
Date:	09/15/2016
HIC/HSC Protocol#:	1608018300
Study Title:	PET Imaging of Synaptic Density in Alzheimer's Disease
Submission Type:	Initial Application
Committee Action:	**Approval**
Committee Action Date:	09/14/2016
Expiration Date:	09/13/2017

Your request regarding the above-referenced protocol has been APPROVED following a review by the convened Institutional Review Board (IRB) at a meeting held on the Committee Action Date noted above. This review meets approval criteria set forth in 45 CFR 46.111. **It is the investigator's responsibility to apply for reapproval prior to the Expiration Date noted above.**

Please note the Review Comments listed below that relate to the review of this study.

Review Comments:

- The Committee has determined that this protocol presents greater than minimal risk to subjects. The protocol attempts to minimize risks to subjects, and the foreseeable risks are reasonable in relation to the potential benefits.

- This protocol was reviewed in accordance with 45 CFR 46.111(b), and appropriate safeguards are in place to protect the welfare of this population considered to be decisionally impaired.

- The Committee acknowledges that this study involves the use of an investigational radiotracers, [11C]APP311 and [11C]PIB, that will be reviewed and approved under the purview of the RDRC, per 21 CFR 361.1. It is the Principal Investigator's responsibility to promptly inform the HIC if the RDRC requires changes to the protocol, and to submit a protocol amendment request accordingly. A copy of the letter from the RDRC approving this protocol must be submitted to the HIC Office. The PI is advised that the HIC will not release the consent documents until receipt of the RDRC approval letter.

- The Principal Investigator is reminded that this study must be submitted to the Yale University Radiation Safety Committee (YURSC) for review and approval of the research-related PET scans described in the study procedures. YURSC approval should be submitted to the HIC for acknowledgment prior to commencing with these procedures. Investigators are advised that if there will be a change in approved radiation use (e.g., an increase in the dose or number of research-related scans per subject), a modification needs to be submitted to the HIC and approved by both the HIC and the RSC prior to implementation.

- The IRB has reviewed the NIA grant #1R01AG052560 (IRES 16-004476) and found it to be consistent with research activities described in the protocol.

- The HIC recognizes that protected health information (PHI) will be collected from potential subjects via telephone screen, and approves a waiver of HIPAA Authorization for Research to allow for verbal authorization for the use of this PHI to determine subject eligibility. The HIC finds that this activity meets the criteria for waiver of documentation of HIPAA research authorization and for waiver of documentation of informed consent, pursuant to 45 CFR §164.512(i)(2) and 45 CFR §46.117(c)(2), respectively.

- All additional recruitment materials should be submitted to the HIC for review and approval prior to use.

- The HIC acknowledges receipt and review of study main points, study blurb, and patient and next of kin assessments.

- The HIC application and compound authorization forms (3) are approved with this submission. The compound authorization forms will be released once RDRC approval has been received.

Amendments: If you wish to change any aspect of this study, such as the study procedures or processes, the informed consent document(s), recruitment activities, or wish to add or remove investigators or key study personnel, you must communicate your requested changes to the HIC using the appropriate form located at http://www.yale.edu/hrpp. Any changes must be approved by the HIC prior to implementation.

Request for Reapproval: It is the investigator's responsibility to obtain reapproval of ongoing research prior to the Expiration Date. Please submit the request for reapproval form 100FR5R at least two months prior to the expiration date to allow for reapproval processing and review.

*Should the research activities no longer involve human participants and you are only conducting data analysis of anonymous de-identified data (with no link to identifiers), IRB approval is no longer required but the IRB does require notification via submission of a closure form 100FR5C.

Request to Close: When the study procedures and the data analysis are fully complete, the Form100FR5C must be completed and sent to the HIC requesting that the study be closed. Investigators should attach a copy of the study findings. Abstracts or publications satisfy this findings requirement.

Adverse Events/UPIRSOs: Serious, unanticipated, and related adverse events, and unanticipated problems involving risk to subjects or others must be reported generally within 5 days of the PI becoming aware of the event (see **Policy 710: Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events**).

Please keep this memo with your copy of the approved protocol documents.

Yale University

Human Investigation Committee
Human Subjects Committee
25 Science Park – 3rd Fl., 150 Munson St.
New Haven CT 06520-8327

Telephone: 203-785-4688
http://www.yale.edu/hrpp

APPROVAL OF SUBMISSION VIA FULL BOARD REVIEW

February 20, 2017

Christopher Van Dyck
203-764-8100
christopher.vandyck@yale.edu

Dear Christopher Van Dyck:

On 2/8/2017, the Yale Institutional Review Board (IRB) reviewed the following submission:

Type of Review:	Modification/Update
Title of Study:	PET Imaging of Metabotropic Glutamate Receptor Subtype 5 in Individuals With and at Risk for Alzheimer's Disease
Investigator:	Christopher Van Dyck
Protocol ID:	1410014799
Submission ID:	MOD00000832
Documents:	• HIC Protocol 30Jan17, Category: IRB Protocol; • RDRC Application 1.23.17, Category: Drug Attachment; • Hyacinth_Human Subject Protection Training, Category: Training certificates; • RDRC Letter 1.2.17, Category: Drug Attachment; • RDRC Response Letter 1.23.17, Category: Drug Attachment; • YU RSC Approval 7.9.16, Category: Drug Attachment;

The Yale IRB approved this submission following a full board review. This approval is valid from 2/8/2017 to 1/7/2018 inclusive.

Review Comments:

The approved amendment revises the repeat scanning protocol in this study to a possibility for one repeat scan (instead of two) and moves information regarding unknown allergies from the radiation risk section, giving it its own section per the request of RDRC. The approved amendment also adds the following non-consenting personnel: Nabeel Nabulsi, Henry Huang, Kelly Rogers, and Ting Xiao.

The Committee has determined that the amendment does not change the assessment of greater than minimal risk for this protocol. The benefits continue to outweigh the risks.

The Committee acknowledges that this study involves the use of investigational radiotracers, [18F]-FPEB and [11C]-PiB, reviewed under the purview of the RDRC, per 21 CFR 361 and that final approval of this modification is needed. A copy of the letter from the RDRC approving this protocol must be submitted to the HIC Office. The PI is advised that the HIC will not release the revised consent documents until receipt of the RDRC approval letter.

The Principal Investigator is reminded to contact Yale University Radiation Safety Committee (YURSC) to identify if they need to review radiation changes that occur with this amendment. YURSC approval should be submitted to the HIC for acknowledgment prior to commencing with these procedures. Investigators are advised that if there will be a change in approved radiation use (e.g., an increase in the dose or number of research-related scans per subject), a modification needs to be submitted to the HIC and approved by both the HIC and the RSC prior to implementation.

The Committee understands that subjects are currently active on study intervention. The Committee requires that the currently enrolled subjects be re-consented at the next study visit, after release of the revised consent, with the newest version of the Compound Authorization and Consent Form with changes clearly identified.

This protocol was reviewed in accordance with 45 CFR 46.111(b), and appropriate safeguards are in place to protect the welfare of this population considered to be decisionally-impaired.

The HIC protocol is approved and validated.

By 11/8/2017, you are to submit documentation for a continuing review. You can request a continuing review by navigating to the active study and clicking Create Modification / CR. Alternatively, you can close the study when the study procedures and the data analysis of identifiable data are fully complete. You can submit a closure request by navigating to the active study and clicking Create Modification /CR.

If you wish to change any aspect of this study, such as the study procedures or processes, the informed consent document(s), recruitment activities, or wish to add or remove investigators or study personnel, you must submit a modification to the study. Any changes must be approved by the IRB prior to implementation.

Serious, unanticipated, and related adverse events, and unanticipated problems involving risk to subjects or others must be reported generally within 5 days of the PI becoming aware of the event (see Policy 710: Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events).

In conducting this study, you should refer to and follow the Investigator Manual (HRP-103), which can be found in the IRB Library within the IRB system.

Please keep this letter with your copy of the approved protocol documents.

Sincerely,

Sandra Alfano, Human Investigation Committee II

Dear Applicant:

In the increasingly complex world of scientific publication, concerns about commercial influence and other possible conflicts make it important for authors to disclose all potential sources of bias. Our system of reviewing conflicts of interest aligns with the policies of the American Academy of Neurology and allows donors to judge whether conflicts exist. Please complete this form, referring to the definitions in the beginning regarding commercial entities, compensation, expert witness, and "immediate family member." At first glance, this task may seem onerous, but will likely take less than 10 minutes.

What to expect: You will be asked whether you have disclosures relating to each question (check yes or no) and will be provided a field in which to list the disclosures. Filling out the forms on the next few screens will be easiest if you have a list of the following items regarding your activity (either commercial or non-profit) and that of any immediate family members during the period of your project. Disclosures are required for any dollar amount, except for gifts valued under $1000. Names of commercial and non-profit entities are required along with specific roles, grant numbers for grants, and specific years. No dollar amounts need to be included. Please indicate complete names of sponsors or companies.

DEFINITIONS

Personal compensation:
Serving on a scientific advisory board
Gifts worth more than $1000
Travel funded by a commercial entity
Serving as a journal editor, associate editor, or on an editorial advisory board
Patents held or pending
Royalties from publishing
Honoraria for speaking engagements
Corporate appointments or consultancies
Speakers' bureaus
Clinical, neurophysiology, or imaging studies in your practice and % effort devoted if the result of this paper will benefit your practice, affiliated unit, or a sponsor

Research support:
Commercial research support
Government research support (including funding organization, grant number, and role)
Academic research support not attributed in the manuscript
Support from a non-profit foundation or society
Stock options for serving on a Board of Directors
License fee payments
Royalty payments from technology or inventions

Stocks, stock options, and royalties
Stock options in a company in which you are (were) an investigator
Stock options in medical industry

Legal proceedings
Expert testimony for a legal proceeding on behalf of industry
Affidavit for a legal proceeding on behalf of industry
Witness or consultant for a legal proceeding on behalf of industry

Optional non-financial
Non-financial disclosures you wish to share

Definitions of Terms in Disclosure Agreement
Commercial entity: A for-profit business that manufactures, distributes, markets, sells, or advertises pharmaceutical or scientific products or medical devices.
Compensation: Anything of monetary value including a salary, honorarium, stipend, gift, or payment of travel-related expenses.
Expert witness: A person who has provided expert medical testimony during a trial or administrative hearing, in a deposition or an affidavit, or in any other type of legal proceeding.
"Immediate family member": Any person who would benefit financially from the publication of the manuscript because of their relationship to the author. This includes a member of an applicant's immediate family or anyone else who has a significant relationship with the applicant.

Please provide all financial relationships (and those of your "immediate family members") from the past two years regardless of whether these relationships are related to the project described in your application.

FINANCIAL DISCLOSURE
Personal Compensation from Commercial and Non-Profit Entities that benefits you directly or indirectly. Within the past two years (and during the course of the study under consideration if the study exceeded two years), I or one of my "immediate family members" received personal compensation for the following:

All compensation received during the past two years regardless of the relationship to your project must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

1. Serving on a scientific advisory board or data safety monitoring board. List specific disclosures in the following format: (1) Commercial or non-profit entity (2) Commercial or non-profit entity... If none, please say "None":

None

2. Gifts (other than travel or compensation for consulting or for educational efforts) worth more than USD $1000. List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of gift, (2) Commercial or non-profit entity, brief description of gift... If none, please say "None":

None

3. Funding for travel or speaker honoraria to the individual from a commercial or non-profit entity not included in the study funding [Exclude CME activities and Grand Rounds]. List specific disclosures in the following format: (1) Commercial or non-profit entity, type of payment, (2) Commercial or non-profit entity, type of payment... If none, please say “None”:

None

4. Serving as a journal editor, an associate editor, or editorial advisory board member. This may include a journal published by your national medical/scientific organization. Please include regardless of whether you receive compensation. List specific disclosures in the following format: (1) Full journal name, role, year(s), (2) Full journal name... If none, please say “None”:

None

5. Patents issued or pending. List specific disclosures in the following format: (1) Brief description of invention/technology, (2) Brief description of invention/technology... If none, please say “None”:

None

6. Publishing Royalties (do not include honoraria for occasional writing). List specific disclosures in the following format: (1) Full title of work, full name of publisher, year(s) of publication (or receipt of royalties), (2) Full title of work... If none, please say “None”:

None

7. Employment. If you are currently employed by a commercial entity, please disclose below. In addition, if your past employment at a commercial entity is directly related to this manuscript, please disclose below. List specific disclosures in the following format: (1) Commercial entity, position, years (2) Commercial entity, position, years... If none, please say “None”:

None

8. Consultancies. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

9. Speakers' bureau. List specific disclosures in the following format: (1) Commercial or non-profit entity, (2) Commercial or non-profit entity... If none, please say “None”:

None

10. Other activities not covered in designations above (if in doubt, provide full disclosure). List specific disclosures in the following format: (1) Commercial or non-profit entity, brief description of activity, (2) Commercial or non-profit entity... If none, please say “None”:

None

11. Some studies have potential for financial gain for the project investigators or the sponsor. The following question seeks to provide transparency regarding any financial benefits to investigators or sponsors.

Do you perform clinical procedures or imaging studies in your practice or unit that overlap with the content of your proposed project, practice parameter, or clinical practice guideline and would your sponsor or this part of your practice or unit benefit if the conclusions were widely followed?
Note: This is the only item in this Agreement that applies to an interest that is related specifically to this particular study, practice parameter, or clinical practice guideline.

List specific disclosures in the following format: (1) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g. 35%), year(s), (2) Name of Practice or Research Unit, Clinical procedure/imaging study, % of effort (e.g., 35%)... If none, please say “None”:

None

RESEARCH SUPPORT
Within the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" received financial or material research support or compensation from the following:

All support received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only support relevant to the topic of the study needs to be disclosed.

12. Commercial entities. List specific disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

13. Government entities. List specific disclosures in the following format: (1) Sponsor/funding source, grant number(s), role, year(s), (2) Sponsor/funding source... If none, please say “None”:

1. Department of Veteran's Affairs, VISN1 Innovations Grant, Project Director/Junior PI, 12/1/2014 - 6/1/2016
2. NIH/NIMH, R25 5R25MH071584, Fellow, 7/1/2014-6/30/2016

14. Academic entities other than those attributed in the manuscript. List specific disclosures in the following format: (1) Academic entity, (2) Academic entity... If none, please say “None”:

Yale University, Department of Psychiatry

15. Foundations or societies (include grant number if required by funding agency). List specific disclosures in the following format: (1) Full name of Foundation or Society, (2) Full name of Foundation or Society... If none, please say “None”:

1. John A. Hartford Foundation (Hartfor Change AGEnts Action Award)

STOCK, STOCK OPTIONS & ROYALTIES

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members":

All revenues during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only revenues relevant to the topic of the study needs to be disclosed.

16. Stock or stock options or expense compensation for serving on a board of directors. List disclosures in the following format: (1) Commercial entity, (2) Commercial entity... If none, please say “None”:

None

17. License fee payments. List specific disclosures in the following format: (1) Invention/technology, source of payment, (2) Invention/technology... If none, please say “None”:

None

18. Royalty payments or have contractual rights for receipt of future royalty payments from technology or inventions (this does not include royalties from publishing). List specific disclosures in the following format: (1) Technology/invention, source of payment, year(s), (2) Technology/invention... If none, please say “None”:

None

19. Stock or stock options in a commercial entity sponsoring research with which the author or "immediate family member" was involved as an investigator (Excludes investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

20. Stock or stock options in a commercial entity whose medical equipment or other materials related to the practice of medicine. (Exclude investments in mutual funds held by the author or dependents). List specific disclosures in the following format: (1) Company, year(s), (2) Company, year... If none, please say “None”:

None

LEGAL PROCEEDINGS

In the past two years and during the course of the study under consideration if the study exceeded two years, I or one of my "immediate family members" have (whether or not it pertains to the topic of the current study):

All compensation received during the past two years regardless of the relationship to the study must be disclosed; for the period exceeding two years, only compensation relevant to the topic of the study needs to be disclosed.

21. Given expert testimony, acted as a witness or consultant, or prepared an affidavit for any legal proceeding involving a commercial entity (do not include proceedings for individual patients). You may specify role, e.g., 'expert witness for plaintiff' if desired. (Include year only if activity is directly related to the present study.)

List specific disclosures in the following format: (1) Commercial entity, activity, year(s), (2) Commercial entity, activity, year(s)... If none, please say “None”:

None

OPTIONAL: NONFINANCIAL DISCLOSURE

22. I have chosen to declare one or more non-financial competing interests (e.g., special interest groups you represent or others that may be affected if your paper is published or that could be perceived as biasing the study; the corresponding author should be aware of conflicts of interest that Co-investigators or Contributors may have). Non-financial disclosures will not be published.

List specific disclosures, if none, please say “None”:

None

☑ I have completed this Disclosure Statement fully and to the best of my ability. I understand that all Applicants must complete this Disclosure Statement and that the information disclosed may be published if their project is accepted for crowdfunding.

By my electronic signature, I verify the completeness and accuracy of the contents of this form.

Click in the box above to add your electronic signature

03/23/2017

Date [MM/DD/YYYY]

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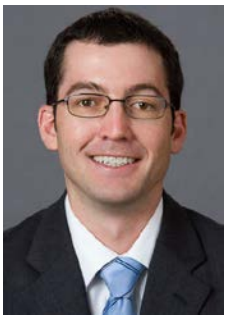

Adam P. Mecca, M.D., Ph.D.

Contact Information

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Alzheimer's Disease Research Unit
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Education/Training

2016 – Present Yale School of Medicine Department of Psychiatry
Geriatric Psychiatry Fellow
Alzheimer's Disease Research Unit, Clinical Research Fellow

2012 – 2016 Yale School of Medicine, Department of Psychiatry
Adult Psychiatry Resident
Neuroscience Research Training Program (2012-2016)
Alzheimer's Disease Research Unit, Chief Resident (2016)

2005 – 2012 University of Florida College of Medicine, M.D. - Ph.D. Program
Graduation with honors in Academic Excellence, Research, and Special Achievement
Dissertation Research: Targeting the ACE2/Ang-(1-7)/Mas Axis for Cerebroprotection during Ischemic Stroke
Mentors: Colin Sumners Ph.D. and Michael J. Katovich, Ph.D.

2001 – 2005 University of Florida – B.S., Highest Honors
Double Major: Chemistry, Microbiology and Cell Science

Honors

2015 American Association for Geriatric Psychiatry Honors Scholar
2014 NIMH Outstanding Resident Award
2014 American Psychiatric Association - Janssen Research Scholars Award
2014 AGS Annual Meeting – Case Studies Poster Presentation Honorable Mention
2012 Dr. Peter Regan Award in Psychiatry – University of Florida
2011 Experimental Physiology Early Career Author Prize
2011 Hazel Donegan Scholarship Award
2010 UF Medical Guild Graduate Student Research Competition, Silver Medal
2010 Florida American Legion Medical Scholarship, Runner-up
2009 Florida Medical Association Foundation Medical Student Scholarship
2009 American Medical Association Foundation Seed Grant

2009	Bryan Robinson Neuroscience Endowment Grant
2009	The Gareth Kerr Memorial Scholarship Award
2009	HHMI – Science for Life Graduate Student Mentor Award
2008	Bryan Robinson Neuroscience Endowment, Honorable Mention
2008	Clinical Translational Science Institute Graduate Student Grant
2008	HHMI – Science for Life Graduate Student Mentor Award
2008	McKnight Brain Institute Graduate Student Investigators Research Grant
2008	UF College of Medicine, Equal Access Clinic Service Award
2007	UF Medical Guild Research Incentive Award
2007	University of Florida College of Medicine Distinguished Service Award
2006	Aurther K. Woodman Scholarship Recipient
2005	Endocrine Society Summer Research Fellowship
2004	Alachua County Fire Rescue Reserves Distinguished Service Award
2004	McLaughlin Scholarship Recipient
2004	Anderson Scholar
2004	President's Honor Roll
2003	Hazen E. Nutter Scholarship Recipient
2002	Golden Key National Honor Society Inductee

Professional Organizations and Activities

2015 - Present	**Member, American Association for Geriatric Psychiatry**
2014 – Present	**Psychiatry Clerkship Interview Tutor (Yale School of Medicine, New Haven, CT)**
2014 - Present	**Member, American Psychiatric Association**
2011	**Member, Professionalism Curriculum Implementation Group (UF, College of Medicine, Gainesville, FL)**
2011 - Present	**Alpha Omega Alpha Honor Society**
2011	**Inductee, Gold Humanism Honor Society, Chapman Chapter**
2002 – 2012	**Equal Access Clinic (UF, College of Medicine, Gainesville, FL) – Equal Access Clinic is a network of multidisciplinary student-run free clinics that provides healthcare to the medically underserved.** 2011/2012, 2009/2010, 2008/2009, 2006/2007 Co-Director 2010/2011 Public Relations Officer 2005/2006 MS1 Representative, Equal Access Clinic 2004/2005 Co-Director, Equal Access Support Committee (UF, Pre-med AMSA) 2003/2004 Associate Director, Equal Access Support Committee 2002/2003 Undergraduate Volunteer, Equal Access Support Committee
2008 – 2016	**Society of Student-Run Free Clinics (SSRFC) – SSRFC is an international organization made up of students participating in student-run free clinics. Our mission is to facilitate collaboration between student-run free clinics.** 2012 - 2016 Resident Advisor 2011/2012 Conference Committee Chair 2010/2011, 2011/2012 Information Technology Officer

	2009/2010 Conference Coordinator 2008/2009 Co-founder and member
2008 – 2012	**American Physician Scientist Association (APSA)** 2008/2009, 2009/2010 President, APSA University of Florida Chapter 2008/2009, 2009/2010 University of Florida Institutional Representative 2008/2009, 2009/2010 Membership Committee Member
2008 – 2012	**Medical Student Selection Committee, University of Florida** 2008-Present Member, MD-PhD Program Student Selection Committee 2011/2012 Member, Medical Student Selection Committee
2009, 2011	**Teaching Assistant, Medical Neuroscience** Spring neurobiology/neuroanatomy course for first year medical students
2008 – 2009	**Citizens for Social Justice (Gainesville, FL)** Co-Director, Medical Affairs, Citizens for Social Justice
2003 – 2005	**Alachua County Fire Rescue – Reserves (Gainesville, Florida)** 2004/2005 Bike Team Leader, Alachua County Fire Rescue Reserves 2003/2004 Volunteer, Alachua County Fire Rescue Reserves

Research Experience

2012 – 2016	Neuroscience Research Training Program (Department of Psychiatry, Yale University School of Medicine)
2008 – 2012	NIH/NINDS Predoctoral Fellow (Department of Physiology and Functional Genomics, University of Florida) – F30 Recipient
2007	Graduate Research Assistant (Department of Physiology and Functional Genomics, University of Florida)
2006	NIH Medical Science Research Program Fellow (Department of Pharmacodynamics, University of Florida)
2005	Endocrine Society Summer Research Fellow (Department of Pharmacodynamics, University of Florida)
2003 – 2005	Laboratory Technician (Department of Pharmacodynamics, University of Florida)
2002 – 2003	Undergraduate Research Student (Department of Pharmacodynamics, University of Florida)

Grant Support

VISN1 Innovation Grant. "Screening Program for Identifying Needs due to Geriatric Syndromes in Homeless Veterans (SPRING). 2014-2015 Co-Author: Adam Mecca, Co-PIs: Marcia Mecca, Theddeus Iheanacho.

Hartford Change AGEnts Action Award. "SPRING: Screening Program for Identifying Needs due to Geriatric Syndromes in Homeless Veterans. 11/2014 – 4/2016 Co-Author: Adam Mecca, Co-PIs: Marcia Mecca, Theddeus Iheanacho.

Thomas P. Detre Fellowship Award in Translational Neuroscience Research in Psychiatry. "Functional Connectivity Alterations and Related Changes in Glutamate Receptor Subtype 5 in Individuals with and at risk Alzheimer's Disease." 2014. PI: Adam Mecca

NIH/NINDS, F30 060335-01A1. "Cerebroprotection via viral-mediated gene delivery of angiotensin AT2 receptors." MD-PhD student individual Fellowship. PI: Adam Mecca; Sponsors: Colin Sumners and Michael Katovich. 7/01/2008 – 06/30/2012.

American Heart Association, Greater Southeast Affiliate 09GRNT2060421. "Angiotensin (1-7) induced cerebroprotection." Co-Author: Adam Mecca; PI: Colin Sumners. 7/01/2009 - 6/30/2011.

AAMC Caring for the Community Grant. "Equal Access Clinic." Author and Project Manager. 7/2008-7/2012.

AMA Foundation Fund for Better Health Grant. "Equal Access Clinic." Author and Project Manager. 7/2008 – 7/2009.

Publications and Presentations:

Mecca AP, Wang S, Barcelos NM, Planeta-Wilson, B, Gelernter J, Van Ness, P, Carson R, van Dyck CH,. Amyloid-Beta Burden is Inversely Associated with Gray Matter Volume but not Episodic Memory Performance in Cognitively Normal First-Degree Relatives at Risk for Alzheimer's Disease. (Under Review)

Mecca AP, Michalak H, McDonald J, Pugh E, Becker M, Kemp E, Zhao H, van Dyck CH. Sleep Disturbance and Risk of Cognitive Decline in the ADNI Cohort. (in preparation)

Thomas JM, Mecca MC, Niehoff K, **Mecca AP**, Van Ness PH, Hyson A, Brienza R, Jeffery S. Development and Validation of a Polypharmacy Knowledge Assessment for Post-Graduate Primary Care Trainees. (in preparation)

Mecca MC, **Mecca AP**. "Principles of Care for the Hospitalized Geriatric Patient." *The Hospital Neurology Book.* Ed. Arash S, Ed. Biller J. New York: McGraw-Hill Education, 2016. Print.

Fineberg SK, **Mecca A**, Lerner Ab BA, Hills OF, Corlett PR, Viron M. Idiom use in a young man with schizophrenia and prominent sexual delusions. Harv Rev Psychiatry. 2014 Sep-Oct;22(5):306-15.

Bennion DM, Regenhardt RW, **Mecca AP**, Sumners C. "Mas and Neuroprotection in Stroke." *The Protective Arm of the Renin-Angiotensin System: Functional Aspects and Therapeutic Implications.* Ed. Unger T, Ed. Steckelings UM, Ed. Santos R. Elsevier, Academic Press, 2015. Print.

Joseph JP, **Mecca AP**, Regenhardt RW, Bennion DM, Rodriguez V, Desland F, Patel NA, Pioquinto DJ, Unger T, Katovich MJ, Steckelings UM, Sumners C. The angiotensin type 2 receptor agonist Compound 21 elicits cerebroprotection in endothelin-1 induced ischemic stroke. *Neuropharmacology*. 2014 Jun;81:134-41.

Regenhardt RW, **Mecca AP**, Desland F, Ritucci-chinni PF, Ludin JA, Greenstein D, Banuelos C, Bizon JL, Reinhard MK, Sumners C. Centrally administered angiotensin-(1-7) increases the survival of stroke prone spontaneously hypertensive rats. *Exp Physiol.* 2014 Feb;99(2):442-53.

Regenhardt RW, Desland F, **Mecca AP**, Pioquinto DJ, Afzal A, Mocco J, Sumners C. Anti-inflammatory effects of angiotensin-(1-7) in ischemic stroke. *Neuropharmacology*. 2013 Aug;71:154-63.

Regenhardt RW, Ansari S, Azari H, Caldwell KJ, **Mecca AP**. Utilizing a cranial window to visualize the middle cerebral artery during endothelin-1 induced middle cerebral artery occlusion. *J Vis Exp*. 2013 Feb 22;(72):e50015.

Ansari S, Azari H, Caldwell KJ, Regenhardt RW, Hedna VS, Waters MF, Hoh BL, **Mecca AP**. Endothelin-1 induced middle cerebral artery occlusion model for ischemic stroke with laser Doppler flowmetry guidance in rat. *J Vis Exp*. 2013 Feb 16;(72).

Mecca AP, Regenhardt, RW, O'Connor TE, Joseph JP, Raizada MK, Katovich MJ, Sumners C. Angiotensin-(1-7) is cerebroprotective in a rat model of ischemic stroke. *Exp Physiol*. 2011 Oct;96(10):1084-96. (Cover Image)

Cao W, Glushakov A, Shah HP, **Mecca AP**, Sumners C, Shi P, Seubert CN, Martynyuk AE. Halogenated aromatic amino acid 3,5-dibromo-D-tyrosine produces beneficial effects in experimental stroke and seizures. *Amino Acids*. 2011 Apr;40(4):1151-8.

Ferreira AJ, Santos RA, Bradford CN, **Mecca AP**, Sumners C, Katovich MJ, Raizada MK. Therapeutic implications of the vasoprotective axis of the renin-angiotensin system in cardiovascular diseases. *Hypertension*. 2010 Feb;55(2):207-13.

Cao W, Shah HP, Glushakov AV, **Mecca AP**, Shi P, Sumners C, Seubert CN, Martynyuk AE. Efficacy of 3,5-dibromo-L-phenylalanine in rat models of stroke, seizures and sensorimotor gating deficit. *Br J Pharmacol*. 2009 Dec;158(8):2005-13.

Mecca AP, O'Connor TE, Katovich MJ, Sumners C. Candesartan pretreatment is cerebroprotective in a rat model of endothelin-1-induced middle cerebral artery occlusion. *Exp Physiol*. 2009 Aug;94(8):937-46. (Cover Image)

Grobe JL, **Mecca AP**, Lingis M, Shenoy V, Bolton T, Machado J, Speth RC, Raizada MK, and Katovich MJ. Prevention of angiotensin II-induced cardiac remodeling by angiotensin-(1-7). *Am J Physiol Heart Circ Physiol*. 2007 Feb; 292(2):H736-42.

Mitra A, Katovich MJ, **Mecca A**, Rowland NE. Effects of central and peripheral injections of apelin on fluid intake and cardiovascular parameters in rats. *Physiol Behav*. 2006 Sep 30; 89(2):221-5.

Grobe JL, **Mecca AP**, Mao H, Katovich MJ. Chronic angiotensin 1-7 prevents cardiac fibrosis in DOCA-salt model of hypertension. *Am J Physiol Heart Circ Physiol*. 2006 Jun; 290(6):H2417-23.

Huentelman MJ, Grobe JL, Vazquez J, Stewart JM, **Mecca AP**, Katovich MJ, Ferrario CM, Raizada MK. Protection from the angiotensin II – induced cardiac hypertrophy and fibrosis by systemic lentiviral delivery of ACE2 in rats. *Exp Physiol*. 2005 Sep; 90(5):783-90.

Abstracts:

Mecca MC, Maiaroto M, DeWorsop D, Rodriguez-Guzman J, Hassell C, **Mecca AP**, Iheanacho T. Screening Program to Identify Needs due to Geriatric Syndromes (SPRING): Improving Healthcare for Homeless Adults. *American Association for Geriatric Psychiatry – Annual Meeting*. 2016.

Rodriquez-Guzman J, Maiaroto M, DeWorsop D, Hassell C, Iheanacho T, **Mecca AP,** Mecca MC**.** Utilizing a Direct Assessment to Identify Functional Impairments in Homeless Adults. *American Association for Geriatric Psychiatry – Annual Meeting.* 2016.

Hassell C, Mecca MC, DeWorsop D, Rodriquez-Guzman J, Maiaroto M, Iheanacho T, **Mecca AP.** Characterizing Trajectories of Homelessness in Older Adults. *American Association for Geriatric Psychiatry – Annual Meeting.* 2016.

Hassell C, Mecca MC, DeWorsop D, Rodriquez-Guzman J, Maiaroto M, Iheanacho T, **Mecca AP.** Characterizing Trajectories of Homelessness in Older Adults. *American Association for Geriatric Psychiatry – Annual Meeting.* 2016.

Mecca AP, Wang S, Barcelos NM, Planeta-Wilson B, Gelernter J, Van Ness P, Carson RE, van Dyck CH. Amyloid-Beta Burden is Inversely Associated with Gray Matter Volume but not Episodic Memory Performance in Cognitively Normal First-Degree Relatives at Risk for Alzheimer's Disease. *Alzheimer's Association International Conference.* 2015.

Mecca AP, Fineberg SK, Mecca MC. New onset delusional parasitosis in a 67-year-old woman with undiagnosed mild dementia. *The American Geriatric Society – Annual Meeting.* 2014.

Santisteban MM, Regenhardt RW, Desland F, **Mecca AP**, Shan Z, Raizada MK, Sumners C. (Pro)renin receptor is up-regulated in the intracerebral infarct zone following ischemic stroke in rats. *North Central Florida Chapter SfN Conference. 2012.*

Regenhardt RW, Santiseban MM, Desland F, **Mecca AP**, Raizada MK, Sumners C. Cerebroprotective angiotensin-(1-7) alters the expression of CXCL12, CXCR4, and pro-inflammatory cytokines in the CNS during stroke. *North Central Florida Chapter SfN Conference. 2012.*

Regenhardt RW, Santiseban M, Desland F, **Mecca AP**, Raizada MK, Sumners C. Prorenin receptor up-regulation in the brain following ischemic stroke is blunted by angiotensin-(1-7). *American Physician Scientist Association National Conference*. 2012.

Regenhardt RW, Ritucci-Chinni P, Desland F, Joseph JP, **Mecca AP**, Sumners C. 2011. Angiotensin(1-7) has therapeutic potential in hemorrhagic stroke. *BRAIN 2011 - 25th International Symposium on Cerebral Blood Flow, Metabolism and Function*, Barcelona, Spain. Abs # 1049.

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